REMARKS

The pending Office Action provides the following comments and rejections:

DETAILED ACTION:

1. The Office Action acknowledges applicants' communication of 12/10/01, (Paper No. 11) and withdraws the final Office Action mailed on 10/24/01 in order to reconsider the rejections and apply new art.

Response: Applicants appreciate the efforts of the Office in reconsidering the rejections presented in earlier Office Actions.

2. Texts of U.S. Code sections not included in the present Office Action may be found in earlier Office communications.

Response: This instruction is acknowledged.

CLAIM REJECTIONS

3. Claim Rejection - 35 USC 102(b)

Summary of Rejection: Claim 1 is rejected under 35 USC 102(b) as being anticipated by Patel (US Patent No. 5,358,708). The Office Action asserts that Patel teaches the stabilization of a pharmaceutical formulation of interferon with histidine.

RESPONSE: This specific rejection is moot because applicants have cancelled Claim 1 and added new Claims 11-17. However, applicants assert that for the reasons that follow, new Claims 11-17 are not anticipated by the Patel patent.

MPEP §2131 states that a claim is anticipated under 35 USC § 102 only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference.

There are at least three very significant differences between new Claims 11-17 and the disclosure in the Patel patent. Those differences are in the type of formulation being stabilized, the stabilizing agents used, and the specific interleukin being evaluated.

• **The Patel patent** and each of its **claims are limited to** the stabilization of **aqueous formulations** of proteins; **applicants' disclosure and claims are directed to lyophilized formulations**. In the first sentence of the Patel disclosure (under the heading of Description) Patel states, "This invention relates to methods for the stabilization against decomposition of **aqueous formulations** containing proteins and, more particularly, to increasing the storage lifetime of formulations containing an interferon, a granulocyte macrophage colony-stimulating factor or **an** interleukin.

New Claim 11 of the present application is directed to the stabilization of lyophilized IL-2 muteins using histidine, glycine, and sucrose. The Patel patent is directed to stabilization using histidine and or methionine; neither glycine nor sucrose is mentioned. The interleukin related data presented by Patel is directed to IL-4 not to the stabilization of IL-2.

The Declaration of Dr. Wei Wang is provided as evidence from a skilled practitioner in the art of protein stabilization. In summary, Dr. Wang declares that there are significant differences between aqueous protein stabilization and lyophilized protein stabilization, and an expert working in this technology area would not consider it obvious or necessarily advisable to apply the agents and technology from one stabilization type to the other.

While the claims of the Patel patent may appear broad, his specification provides very limited support for the claims. **The Patel patent** addresses the stabilization of only one interleukin and it **states that histidine does not stabilize IL-4 as well as a control (made up of only a buffer solution)**. Example 3 (copy attached) discusses the stabilization of interleukin (IL-4), saying that "**histidine is considerably less effective (than the control solution at stabilizing IL-4)** under the conditions of this test". Patel provides graphic support in Figure 4 for his statement, which shows that after two weeks, the histidine stabilization of IL-4 was less effective than the control (which contained only citrate buffer). **This statement and graph by Patel is a "teaching away" from stabilization using histidine**, and from the disclosure contained in applicants' application.

In the next example (Example 4) **Patel states** that in evaluating stabilizers of GM-CSF he determined that " ... **glycine is not an effective stabilizer of the GM-CSF protein** for storage at elevated temperatures."

The Patel patent teaches away from the use of histidine as a successful stabilizer of interleukins and teaches away from the use of glycine as an effective stabilizer of GM-CSF.

• **In summary,** there are significant differences between the technology disclosed and claimed by applicants and that disclosed and claimed by Patel. **The Patel patent is focused solely on the stability of aqueous formulations** while **applicants' present application and claims are focused on the stability of lyophilized formulations**. Patel evaluates the stabilization of IL-4 using histidine and teaches away from its use, whereas the present application demonstrates the stabilization of IL-2 using histidine, glycine and sucrose.

While the present basis of rejection is moot because it is directed to cancelled Claim 1, applicants assert that for the reasons presented above **and those contained in the**

attached Declaration of W. Wang, new Claims 11-17 are not anticipated by the Patel patent.

4. Claim Rejection - 35 USC 103(a)

Summary of Rejection: Claims 1-3, 5, and 9 are rejected under 35 USC 103(a) as being unpatentable over Patel (US Patent No. 5,358,708) in view of Hora et al. (US Patent No. 5,078, 997).

The Office Action argues that while Patel does not explicitly recite a pharmaceutical composition comprising human IL-2 or a variant stabilized with amino acids, sucrose and salt; a skilled practitioner (knowing of the Patel patent) would look to Hora et al. who teaches the stabilization of lyophilized IL-2 using those materials and subsequent reconstitution with water.

RESPONSE: This specific rejection is moot because applicants have cancelled Claims 1-3, 5, and 9 and added new claims 11-17. However, for the reasons that follow, applicants assert that new Claims 11-17 are not anticipated by Patel (US Patent No. 5,358,708) in view of Hora et al. (US Patent No. 5,078, 997).

MPEP 2141.02 *states that "In determining the differences between the prior art and the claims, the question under 35 USC 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious."*

• As discussed above, **the Patel patent is focused exclusively on the stability problems associated with aqueous formulations** of proteins (**and only one interleukin, IL-4**) and on Patel's approach to resolving those problems. It is noteworthy that Patel, discusses the stability problems associated with lyophilized proteins, but **he does not even suggest that his aqueous stabilization technology**

can be applied to the stability problems of lyophilized preparations. It is very important to note that in the Patel patent, **the inventor states** (Column 5, lines 13-15) that **histidine is not as effective at stabilizing IL-4 as a control solution (that contained no amino acid agent: see Example 3 and Figure 4).**

In the next example (Example 4) **Patel states** that in evaluating stabilizers of GM-CSF he determined that " ... **glycine is not an effective stabilizer of the GM-CSF protein** for storage at elevated temperatures." The results shown in Example 4 also indicate that when stored at -80° C. glycine was no more effective than the control (described as None) at stabilizing GM-CSF.

In brief, **the Patel patent teaches away from the use of histidine as a successful stabilizer of interleukins, or the use of glycine as an effective stabilizer of the protein GM-CSF.**

• **The Hora patent** (US Patent No. 5,078,997) **is directed to the stabilization of lyophilized IL-2** using materials selected from the group consisting of: arginine/carnitine mixture; carnitine; betaine; pyridoxine polyvinylpyrrolidone; salts of capric acid and mixtures thereof. In additional to this stabilization mixture, Hora adds sugar or sugar alcohol and a buffer, where the buffer is citrate. **Hora makes no reference to using either histidine or to glycine for any purpose.**

• **In Summary - The Patel patent is directed to *aqueous* formulations and *teaches away* from the use of histidine as a successful stabilizer of interleukins, or the use of glycine as a stabilizer of GM-CSF (or any other protein).** The **Hora patent, which is directed to lyophilized formulations, is completely *silent on the use of histidine or glycine* for any purpose.**

While the present basis of rejection is moot because it is directed to cancelled Claims 1 - 3, 5 and 9, applicants assert for the reasons presented above Patel and Yasushi can not be properly combined to make new Claims 11-17 ***as a whole obvious."***

5. Claim Rejection - 35 USC 103(a)

Summary of Rejection: Claims 1-3, 5, and 9 are rejected under 35 USC 103(a) as being unpatentable over Patel (US Patent No. 5,358,708) in view of Hora et al. (US Patent No. 5,078, 997) in view of Yasushi et al. (U.S. Patent No: 4,645,830).

The Office Action argues that while Patel does not explicitly recite a pharmaceutical composition comprising human IL-2 or a variant stabilized with amino acids, sucrose and salt; a skilled practitioner (knowing of the Patel patent) would look to Hora et al. who teaches the stabilization of lyophilized IL-2 using those materials and subsequent reconstitution with water, and Yasushi teaches the loss of activity due to lyophilization is minimized in stabilized IL-2..

RESPONSE: This specific rejection is moot because applicants have cancelled Claims 1-3, 5 & 9 and added new claims 11-17. However, for the reasons that follow, new Claims 11-17 are not anticipated by Patel (US Patent No. 5,358,708) in view of Hora et al. (US Patent No. 5,078, 997) in view of Yasushi et al. (U.S. Patent No: 4,645,830).

MPEP 2141.02 *states that "In determining the differences between the prior art and the claims, the question under 35 USC 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious."*

• The Yasushi et al. patent (U.S. Patent No: 4,645,830) teaches (Column 1, lines 24-28) a **stable** IL-2 composition comprising IL-2 and either **human serum albumin** (HSA), **a reducing compound, or both**. Yasushi states, "**The reducing compound is** said to be preferably a physiologically acceptable reducing compound and thus includes sulfur-containing reducing compounds such as glutathione (reduced form; hereinafter simply glutathione), thioctic acid, N-acetylcysteine, N-

acetylhomocysteine, thiodiglycol, thioethanolamine, monothioglycerol,dithiothreitol and thioalkanoic acids containing 1-7 carbon atoms (e.g. thioglycolic acid, thiomalic acid), and ascorbic acid and salts thereof, or mixtures thereof. Preferred are acidic compound such as glutathione, thioctic acid, N-acethylcysteine and ascorbic acid, and particularly preferred are glutathione and ascorbic acid." **These are the only components that Yasushi teaches as being a part of his *stabilized* IL-2 compound.**

As the Office Action observes, **Yasushi says (Column 2, lines 50-63) that his composition may contain one or more *additional* substances** along with the **human serum albumin**. According to Yasushi, those additional substances may include amino acids (especially monoamino aliphatic amino acids, cyclic amino acids and glycine), monosaccharides such as glucose and mannose, alcohols such as sorbitol and mannitol, and physiologically acceptable salts and derivatives thereof. **But the Office Action does not identify any teaching from the patent regarding the purpose or function of these "additional substances."**

In Column 4, lines 7-22, Yasushi explains why "additional substances" may be added to the composition. He states, "Among those IL-2 compositions provided by the invention, the lyophilizate in the form of a stabilized IL-2 powder ... may be used advantageously as a preparation for parenteral administration. In using as a preparation for injection, the lyophilizate is dissolved in 0.5-100 ml of distilled water, physiological saline, or in 0.5-100 ml of a solvent attached to the lyophilizate composition. ***When the lyophilizate is dissolved in a solvent, the solvent is preferably an aqueous solution of an amino acid such as glycine*, a *monosaccharide*** such as glucose or a sugar alcohol such as mannitol. The pH is adjusted as necessary, and the solution is administered intramuscularly or intravenously. Said composition may also be used in the form of preparations for administration into the oral and nasal cavity or to the eye or ear by using an appropriate carrier, excipient or diluent." In brief, **Yasushi is stating that the glycine (and monosaccharide) is useful in dissolving the lyophilizate in water, not in stabilizing the compound.** Lastly, **the sugar found in applicants' invention is**

sucrose, which is a disaccharide, and therefor different from the Yasushi sugars.

The Yasushi patent (in the Examples section) addresses two aspects of the technology: **potency** and **solubility**. **In each of the Examples** that relate to the use of glycine (Examples 6, 8, 10, 11) **potency of the IL-2 compound does not noticeably change, but solubility does change**. This further explains that **role of glycine in Yasushi's patent is as an agent to improve solubility** of the IL-2 compounds (not stability).

The conclusion that must follow from this review of the Yasushi patent is that the inventor is teaching the use of glycine as an agent to improve solvent solubility. If the inventors of the present application had reviewed Yasushi patent, the teaching they would have seen is that when added to the solvent, glycine can influence lyophilizate solubility. However, **since the present application is directed to stabilization of lyophilized compounds**, and not to solubility or liquid formulations, **the teaching of Yasushi regarding glycine would have been irrelevant to the inventors of the pending application.**

• As was discussed above, **the Patel patent** is directed to *aqueous* formulations and *teaches away* from the use of histidine as a successful stabilizer of interleukins, or the use of glycine as a successful stabilizer of one protein. **The Hora patent**, which is directed to *lyophilized* formulations, is completely *silent on the use of_histidine or glycine* for any purpose. *And* in **the Yasushi patent**, the inventor teaches that glycine is useful to improve *solubility*, but he is silent on the use of glycine to improve or establish the stability of any interleukin.

While the present basis of rejection is moot because it is directed to cancelled Claims 1-3, 5 & 9, applicants assert for the reasons presented above Patel, Hora, and Yasushi can not be properly combined to make new Claims 11-17 ***as a whole obvious."***

6. **Claim Rejection - 35 USC 103(a)**

Summary of Rejection: Claims 1-6, 9 and 10 are rejected under 35 USC 103(a) as being unpatentable over Patel (US Patent No. 5,358,708) in view of Hora et al. (US Patent No. 5,078, 997) in view of Yasushi et al. (U.S. Patent No: 4,645,830) and further in view of Shanafelt (WO 9960128A1).

The Office Action states that the relevance of the Patel, Hora and Yasushi patents has been set forth above. The Office Action then argues that while these prior references do not explicitly recite the use of the IL-2 variant (N88R) in a pharmaceutical composition, Shanafelt does recite an IL-2 (WO 9960128A1). The Office Action then concludes that it would have been obvious to one of skill in the art to combine the teachings of Patel, Hora and Yasushi to the disclosure of Shanafelt to produce Claims 1-6, 9 and 10 of applicants' invention.

RESPONSE: This specific rejection is moot because applicants have cancelled Claims 1-6, 9-10, and added new claims 11-17. However, for the reasons that follow, applicants assert that new Claims 11-17 are not anticipated by Patel (US Patent No. 5,358,708) in view of Hora et al. (US Patent No. 5,078, 997) in view of Yasushi et al. (U.S. Patent No: 4,645,830) and further in view of Shanafelt (WO 9960128A1).

MPEP 2141.02 *states that "In determining the differences between the prior art and the claims, the question under 35 USC 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious."*

New Claims 11-17 are directed to a stabile **lyophilized formulation** of an IL-2 mutein that include **histidine, glycine,** and **sucrose**.

• **The Shanafelt application** (WO 9960128A1) discloses IL-2 muteins including the N88R variant. However, **Shanafelt is silent on any stabilizing formulation**.

• **The Patel patent is focused exclusively on** the stability problems associated with **aqueous formulations** of proteins (and only one interleukin, IL-4) and on Patel's approach to resolving those problems. It is noteworthy that **Patel** discusses the problems of lyophilized formulations, but **does not even suggest that his aqueous stabilization technology can be applied to lyophilized formulations**.

It is important to note that **Patel states** (Column 5, lines 13-15) that **histidine is not as effective at stabilizing IL-4 as was a control solution (that contained no amino acid agent: see Figure 4).** In Example 4, **Patel states that in evaluating stabilizers of GM-CSF he determined that " ... glycine is not an effective stabilizer of the GM-CSF protein for storage at elevated temperatures."**

In summary, the Patel patent is limited to the stabilization of aqueous formulations, it **teaches away from the use of histidine as a successful stabilizer of interleukins**, and **teaches that glycine is not an effective stabilizer of the GM-CSF protein** (and is silent on the use of glycine to stabilize any other protein).

• **The Hora patent** (US Patent No. 5,078,997) **is directed to the stabilization of lyophilized IL-2** using materials selected from the group consisting of: arginine/carnitine mixture; carnitine; betaine; pyridoxine polyvinylpyrrolidone; salts of capric acid and mixtures thereof. In additional to this stabilization mixture Hora adds sugar or sugar alcohol and a buffer, where the buffer is citrate. **Hora makes no reference to either histidine or to glycine for any purpose, let alone stabilizing lyophilized IL-2 muteins.**

• **The Yasushi et al. patent** (U.S. Patent No: 4,645,830) **teaches** (Column 1, lines 24-28) a **stable IL-2 composition stabilized with** either **human serum albumin** (HSA), **a reducing compound, or both. These are the only components that Yasushi teaches** as being a part of his **stabilized** IL-2 compound.

As was discussed above, Yasushi does not mention the use of glycine as a stabilizing agent. Instead, **Yasushi discusses glycine (Column 4, lines 7-22) as being useful in dissolving the lyophilizate in water.**

The conclusion that must follow from this review of the Yasushi patent is that the inventor is teaching the use of glycine as an agent to improve solubility. Had the inventors of the present application read the Yasushi patent, the teaching they would have seen is that glycine can influence solubility. However, **since the present application is directed to stabilization of lyophilized compounds**, and not to solubility or liquid formulations, **the teaching of Yasushi regarding glycine would have been irrelevant to their research efforts**.

• **Summary - As discussed above, the Patel patent relates only to aqueous formulations and teaches away from the successful use of histidine as a stabilizer of interleukins**, and teaches that glycine is not an effective stabilizer of the GM-CSF protein. The **Hora** patent **makes no reference to either histidine or to glycine for any purpose**. The **Yasushi patent teaches** IL-2 stabilized with human serum albumin (HSA), a reducing compound or both, but mentions **glycine only as being useful in dissolving the lyophilizate in water. Because none of these patents encourage the use of histidine or glycine for lyophilized interleukin stabilization, the present applicants could not have relied upon Patel, Hora and Yasushi, in view of Shanafelt to produce the present claimed invention.**

While the present basis of rejection is moot because it is directed to cancelled Claims 1-6, and 9-10, applicants assert for the reasons presented above Patel, Hora, and Yasushi can not be properly combined with Shanafelt to make new Claims 11-17 ***as a whole*** *obvious."*

In conclusion, applicants believe that new Claims 11 - 17 are in condition for allowance, and each of the grounds of objection and rejection presented by the Office has been addressed and prompt issuance of the present case is earnestly solicited.

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call their Attorney at the phone number listed below.

Respectfully Submitted,

John W. Mahoney 9/27/02

Attorney for Applicants
John W. Mahoney
Reg. No. 44, 892

Bayer Corporation
Law and Patent Department
800 Dwight Way
P.O. Box 1986
Berkeley, CA 94701
(510) 705-7901